Rationale and design of the Onyx ONE global randomized trial: A randomized controlled trial of high-bleeding risk patients after stent placement with 1 month of dual antiplatelet therapy

Elvin Kedhi, MD, PhD,[a] Azeem Latib, MD,[b] Alexandre Abizaid, MD,[c] David Kandzari, MD,[d] Ajay J. Kirtane, MD, SM,[e] Roxana Mehran, MD,[f] Matthew J. Price, MD,[g] Daniel Simon, MD,[h] Stephen Worthley, MD,[i] Azfar Zaman, MD,[j] Sandeep Brar, MD,[k] Minglei Liu, PhD,[k] Gregg W. Stone, MD,[e] and Stephan Windecker, MD[l] *Zwolle, the Netherlands; New York, NY; São Paulo, Brazil; Atlanta, GA; La Jolla, Santa Rosa, CA; Cleveland, OH; Adelaide, Australia; Newcastle upon Tyne, UK; and Bern, Switzerland*

Abstract Background and Rationale Polymer-free drug-eluting stent (DES) implantation in combination with 1-month dual antiplatelet therapy (DAPT) has shown superior safety and efficacy outcomes compared with bare-metal stents among patients with high-bleeding risk (HBR) treated with 1-month DAPT. The safety and efficacy of the newer-generation durable-polymer DES Resolute Onyx compared with polymer-free DES among HBR patients treated with 1-month DAPT is unknown.

Trial Design The Onyx ONE global randomized trial is an international, prospective, randomized, blinded, controlled study enrolling HBR patients undergoing percutaneous coronary intervention. The trial will randomize up to 2,000 patients in a 1:1 fashion to receive either the durable-polymer Resolute Onyx DES or the polymer-free Biosensors BioFreedom DES. After index procedure, patients in both arms will be treated with 1 month of DAPT (aspirin and oral P2Y12 inhibitor), followed by single antiplatelet therapy thereafter. The primary end point is the composite end point of cardiac death, myocardial infarction, or stent thrombosis at 1-year follow-up. The powered secondary end point is target lesion failure (defined as the composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization) at 1 year. Patient follow-up is planned for 1, 2, and 6 months and 1 and 2 years after the procedure.

Conclusions The Onyx ONE global randomized trial is the first study to directly compare the safety and efficacy of a durable polymer DES (Resolute Onyx) with a polymer-free DES (BioFreedom) in HBR patients treated with 1 month of DAPT. (Am Heart J 2019;214:134-41.)

From the [a]Isala Hartcentrum, Zwolle, the Netherlands, [b]Department of Cardiology, Montefiore Medical Center, New York, NY, [c]Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil, [d]Piedmont Atlanta Hospital, Atlanta, GA, [e]Columbia University Medical Center/NewYork-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, NY, [f]Department of Cardiology, Mount Sinai Medical Center, New York, NY, [g]Department of Cardiovascular Diseases, Scripps Clinic, La Jolla, CA, [h]University Hospitals Cleveland Medical Center, Cleveland, OH, [i]Royal Adelaide Hospital, Adelaide, Australia, [j]Freeman Hospital and Newcastle University, Newcastle upon Tyne, UK, [k]Medtronic, Santa Rosa, CA, and [l]Department of Cardiology, Swiss Cardiovascular Center, Bern University Hospital, Bern, Switzerland.

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Reprint requests: Elvin Kedhi, MD, PhD, Isala Hartcentrum, Isala Klinieken, Docter Van Heesweg Nr. 2, Zwolle, the Netherlands.

E-mail: e.kedhi@isala.nl

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The duration of dual antiplatelet therapy (DAPT) after coronary artery stenting has been a topic of debate for several decades. Although 1-month DAPT in patients receiving bare-metal stent (BMS) treatment has been considered safe (1,2), the optimal duration of DAPT after drug-eluting stent (DES) implantation is unclear. Concerns with first-generation DES of very late-stent thrombosis (ST) led to recommendations for prolonged DAPT of ≥12-months (3), despite the lack of clinical evidence supporting this approach. Furthermore, newer-generation devices with thinner struts, improved durable polymer biocompatibility, bioabsorbable polymers, or polymer-free DES have significantly reduced major adverse cardiac events (MACEs) such as ST and consequently the need for an extended duration of DAPT. Indeed, several randomized clinical trials of newer-

generation DES did not find an increased risk of stent thrombosis with 3 to 6 months DAPT (4-7). The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend a minimum of 6 and 12 months DAPT for newer-generation DES in non–high-bleeding risk (HBR) patients with stable coronary artery disease and acute coronary syndromes, respectively (8,9).

Although longer DAPT regimens may reduce thrombotic events after stenting and non–stent-related cardiovascular events, prolonged DAPT usage is associated with increased bleeding risk (10). Therefore, HBR patients undergoing percutaneous coronary intervention (PCI) are sometimes treated with BMS in combination with 1 month of DAPT, although this is no longer routinely recommended (9). Shorter DAPT duration (1 month of DAPT with a class IIB, level of evidence C recommendation; 3 months of DAPT with a class IIA, level of evidence B recommendation) may be appropriate for certain HBR patients receiving DES (9); these recommendations were based on recent randomized clinical trials that investigated the impact of shortened DAPT on selected HBR patients after stent implantation, including the Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) (11) and Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trials (12).

ZEUS randomized patients designated as HBR or high thrombotic risk to any BMS or the Endeavor DES (Medtronic, Santa Rosa, CA) (13). HBR and stable high-thrombotic-risk patients were prescribed 1-month DAPT after the procedure. The risk of MACEs at 1 year was significantly lower in the DES group (11). The LEADERS FREE trial randomly assigned HBR patients to the polymer-free BioFreedom (Biosensors Europe, Morges, Switzerland) DES platform or BMS in conjunction with 1-month DAPT (14). Polymer-free DES was superior to BMS for the primary composite end point of cardiac death, myocardial infarction (MI), or ST at 1 year (12). A similar treatment effect with polymer-free DES was observed in various subgroups of the LEADERS FREE trial, including patients older than 75 years (15), with diabetes (16) and with acute coronary syndrome (17), and those requiring chronic oral anticoagulation (18). A third study of relevance is the SENIOR trial, which found that 1 and 6 months of DAPT was safe in elderly patients treated with the Synergy stent (Boston Scientific, Marlborough, MA), which elutes everolimus from a bioabsorbable polymer (19).

Both European Society of Cardiology and American College of Cardiology guidelines acknowledge that there is limited clinical evidence evaluating the optimal duration of DAPT in HBR patients after stent implantation. In particular, there are no data comparing the safety and efficacy of polymer-free DES with newer-generation durable-polymer DES among HBR patients requiring 1-month DAPT. The thin-strutted Resolute Onyx (Medtronic) DES is the latest iteration of the Resolute DES platform and has been commercially available since 2014. The Resolute Onyx shares the identical polymer and drug with previous Resolute stent platforms (20,21), but is formulated from a cobalt alloy wire with a platinum iridium core, enabling thinner struts while maintaining radial strength and radio-opacity. The safety and efficacy of the Resolute DES product family has been demonstrated in more than 17,000 patients enrolled in the RESOLUTE Global Clinical Program, including more than 10 clinical studies and registries. Specifically, in an analysis of 7,618 patients, the Resolute stent demonstrated a low rate of cardiac events and a 1.2% stent thrombosis rate through 5 years of follow-up (22). Furthermore, in a post-hoc analysis of 4,896 patients from the RESOLUTE Global Clinical Program, DAPT interruption between 1 and 12 months after Resolute stent implantation was associated with low rates of stent thrombosis and adverse cardiac outcomes, with the majority of events occurring within the first 30 days (23). Considering the favorable safety and efficacy profile of the Resolute family of DES, it is conceivable that Resolute Onyx may be safe and effective in HBR patients requiring shorter DAPT. Furthermore, Resolute Onyx demonstrated high rates of Optical Coherence Tomography-assessed coverage rate 30 days after implantation, with 92.3% of the total lumen surface area fully covered (24).

In this context, the Onyx ONE global randomized trial was designed to compare the clinical safety and effectiveness of the Resolute Onyx DES with the BioFreedom DES in patients at HBR or medically unsuitable for longer than 1 month of DAPT.

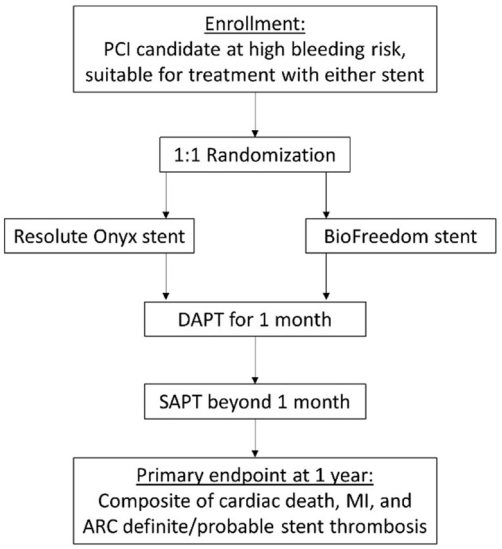
Methods

Trial design

Onyx ONE is a prospective, single-blinded trial planned to randomize up to 2,000 patients at 86 clinical sites in Asia-Pacific and Europe. The trial was designed by the sponsor (Medtronic) in conjunction with the steering committee (listed in the Appendix) and the US Food and Drug Administration. The trial was funded by Medtronic.

The trial design is illustrated in Figure 1. Patients enrolled are eligible for PCI and must meet predefined HBR criteria similar to those in the LEADERS FREE trial (14). All inclusion and exclusion criteria are listed in Table I. Key exclusion criteria include active bleeding at the time of inclusion, cardiogenic shock, PCI during the previous 6 months for a nontarget lesion, planned PCI more than 1 month after index procedure, or any planned surgery/procedure necessitating discontinuation of DAPT within 1 month after the index procedure.

Figure 1



Trial design.

Before randomization, coronary angiography is performed to evaluate coronary anatomy for suitability of stent implantation. Patients will be followed up clinically through 2 years, study exit, or death, whichever comes first. A clinic visit is planned at 1 month with additional follow-up at 2 and 6 months and 1 and 2 years after index procedure. Follow-up data collected include angina status, any adverse events or device deficiency data, and prescribed antiplatelet medications.

The sponsor did not provide stents for free. The sponsor only reimbursed investigational sites for study-specific work not considered standard of care. Enrolled patients received a reasonable travel fee for protocol-required clinic visits.

Randomization and blinding

Randomization occurs before PCI by an interactive web/voice response system. Randomized patients are allocated 1:1 to receive either a durable polymer Resolute Onyx or a polymer-free BioFreedom DES, stratified by study site, diabetes, and MI status using a blocked randomization scheme. There are currently 1,997 patients randomized in the trial.

Patients, clinical site personnel conducting patient follow-ups, and referring/managing physicians are blinded to randomization assignment. To minimize the risk of patient unblinding, site staff are trained not to disclose the implanted stent to the patient and not to mention the stent type in the discharge letter. In addition, the sponsor's clinical study team and the external, independent clinical events committee (CEC) are blinded to randomization assignment. Interventional cardiologists conducting the procedures are not blinded to randomization.

Table I. Inclusion and exclusion criteria for Onyx ONE global study.

Inclusion criteria

- Acceptable candidate for treatment with a DES
- Provide written informed consent
- Meet one of the following criteria for being HBR and/or are candidates for 1-mo DAPT:
  - o Adjunctive oral anticoagulation treatment planned to continue after PCI
  - o Age ≥75 y
  - o Baseline Hgb <11 g/dL (or anemia requiring transfusion during the 4 wk before randomization)
  - o Any prior documented intracerebral bleed
  - o Any documented stroke in the last 12 mo
  - o Hospital admission for bleeding during the prior 12 mo
  - o Nonskin cancer diagnosed or treated ≤3 y
  - o Planned daily NSAID (other than aspirin) or steroids for ≥30 d after PCI
  - o Planned surgery that would require interruption of DAPT (within the next 12 mo)
  - o Renal failure defined as: creatinine clearance <40 mL/mi
  - o Thrombocytopenia (PLT <100,000/mm^3)
  - o Severe chronic liver disease defined as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice
  - o Expected noncompliance to prolonged DAPT for other medical reasonsExclusion criteria
- Pregnant and breastfeeding women
- Patients requiring a planned PCI procedure after 1 mo of index procedure
- Procedure planned to require nonstudy stents, stand-alone balloon angioplasty, or stand-alone atherectomy
- Active bleeding at the time of inclusion
- Cardiogenic shock
- Patient with planned surgery or procedure necessitating discontinuation of DAPT within 1 mo after index procedure
- Patient not expected to comply with long-term SAPT
- A known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, P2Y12 inhibitors, mTOR inhibiting drugs such as zotarolimus, biolimus A9 (or its derivatives), cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (eg, BioLinx), stainless steel (or other metal ions found in 316 L stainless steel), zinc, or a sensitivity to contrast media, which cannot be adequately premedicated
- PCI during the previous 6 mo for a lesion other than the target lesion of the index procedure
- Participation in another clinical study within 12 mo after index procedure
- Patients with life expectancy of <2 y

Abbreviations: Hgb, hemoglobin; NSAID, Nonsteroidal anti-inflammatory drug; PLT, platelet.

Trial organization

The trial is approved by the appropriate ethics review board at each clinical site. All patients will provide written informed consent before enrollment. The trial was designed in accordance with the Declaration of Helsinki. The sponsor of the trial is Medtronic. All centers selected worldwide are experienced in clinical research. Data are collected at each clinical site and stored via electronic case report forms.

Detailed listings of the study committees and participating sites appear in the Appendix. The role of the

steering committee is to advise study design and execution, provide overall supervision of the study, and have responsibility for reviewing the final study results and determining methods of presentation and publication. The CEC will review and adjudicate all deaths and safety end point–related adverse events (Cardiovascular Research Foundation, New York, NY). An external, independent data monitoring committee from Cardiovascular Research Foundation will evaluate safety data and advise the sponsor in regard to continued safety of the study to ensure the well-being of the patients. An independent Angiographic Core Laboratory (Beth Israel Deaconess Medical Center, Boston, MA) will evaluate all angiograms collected at baseline and after any MI, death, revascularization, or stent thrombosis. Study monitors (Medtronic MC2; Minneapolis, MN) will verify patient data and ensure compliance with this Clinical Investigational Plan and other study requirements. The trial is registered at www.clinicaltrials.gov (NCT03344653).

Procedure

Patients receive either Resolute Onyx or BioFreedom stent(s) for treatment of one or more lesions in one or more vessels. Operators are instructed to implant only the assigned stent type during the index procedure and any subsequent staged procedures. If the assigned study stent cannot be placed, operators are recommended to use the comparator device (Resolute Onyx stent or BioFreedom) or another device at their discretion. Predilatation and postdilatation are recommended but not mandated.

If due to clinical reasons a staged procedure is required, it should take place within 1 month from index procedure. Every urgent coronary reintervention before the planned staged procedure will be considered an event. Staged procedures in the target vessel(s) treated at index or a segment directly adjacent to a segment treated during the index PCI are not allowed.

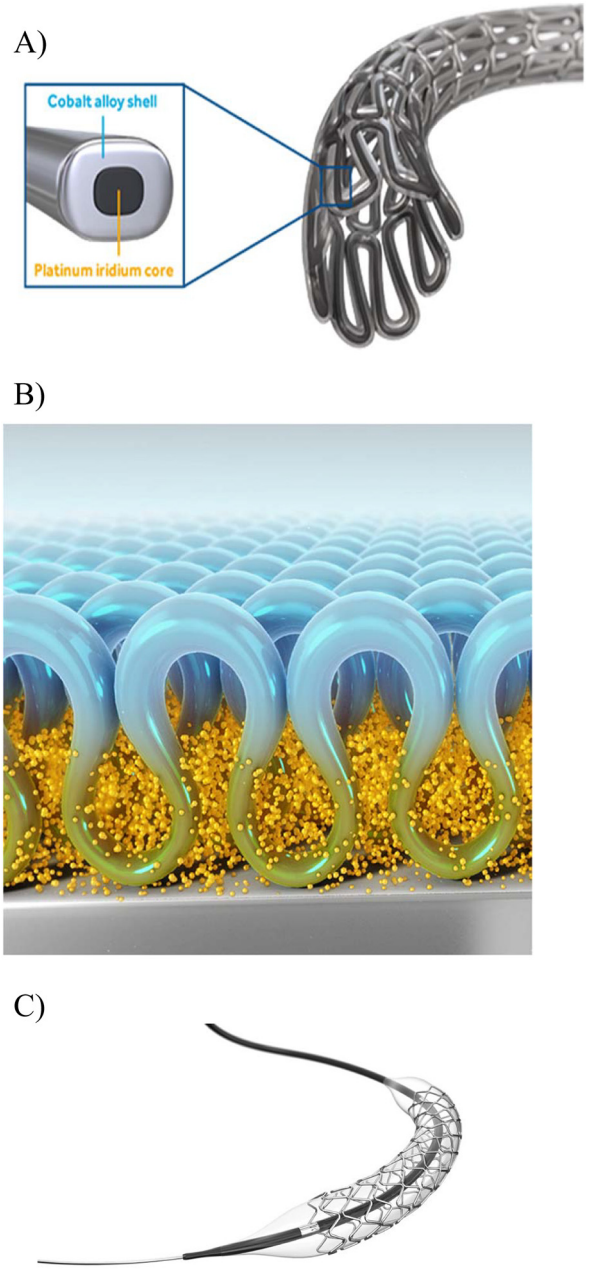
If the procedure involves treating a bifurcation lesion, a single-stent strategy (ie, a provisional stenting technique) is recommended: stent placement in the main branch, finalized with proximal optimization technique, followed by placement of a second stent if inadequate results are found in the side branch (such as threatened closure of the side branch, dissection type B or worse, Thrombolysis in Myocardial Infarction flow <3, or residual stenosis >80%) (25,26).

Intravascular imaging with either ultrasound or optical coherence tomography is allowed per local practice and standard of care.

Resolute Onyx

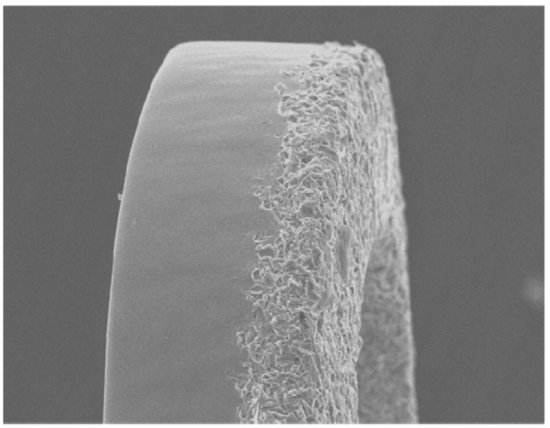
The Resolute Onyx DES is manufactured using a single strand of composite wire with a swaged shape formed into a sinusoidal design, wrapped in helical form around a mandrel, and laser-fused at specific crowns to create its final shape (Figure 2) (20,21). The composite wire comprises an outer shell of cobalt alloy and an inner core of 90% platinum and 10% iridium alloy. The higher density of the platinum/iridium alloy inner core improves

Figure 2



Resolute Onyx DES design. A, A single strand of composite wire is formed into a sinusoidal design, wrapped in helical form around a mandrel, and laser-fused at specific crowns to create its final shape. The composite wire comprises an outer shell of cobalt alloy and an inner core of 90% platinum and 10% iridium alloy. B, The biocompatible BioLinx polymer system is 6 μm thick and consists of a blend of 3 different polymers. C, Resolute Onyx DES is premounted on a semicompliant balloon rapid exchange delivery system.

Figure 3



The textured abluminal surface of the BioFreedom coronary stent, coated with the active ingredient BA9.

visibility under x-ray. The strut shape was designed to increase strut width-to-thickness ratio, which allows for a reduced strut thickness of 81 μm without compromising radial strength.

Zotarolimus, the drug used in Resolute Onyx DES, is a semisynthetic rapamycin derivative with immunosuppressive and antiproliferative properties that arrests the cell cycle in the G1 phase, thereby reducing cell proliferation and neointimal hyperplasia. The biocompatible BioLinx (Medtronic) polymer system is 6 μm thick and consists of a blend of 3 different polymers (hydrophobic C10 polymer, hydrophilic C19 polymer, and polyvinyl pyrrolidinone). The polyvinyl pyrrolidinone is a hydrophilic polymer designed to increase the biocompatibility of the stent (27). Almost 80% of the drug is released by 30 days and completely by 180 days (27). Resolute Onyx DES is premounted on a semicompliant balloon rapid exchange delivery system.

BioFreedom

BioFreedom is a polymer- and carrier-free coronary stent consisting of a 316-L stainless steel stent coated abluminally with umirolimus, also known as biolimus A9, or BA9 (Figure 3) and premounted on a semicompliant rapid exchange balloon delivery system. The strut thickness is 120 μm. BA9 is a semisynthetic sirolimus derivative with high lipophilicity to inhibit smooth muscle cell proliferation within the proximity of the stent.

Antiplatelet medication

Preprocedure, a loading dose of aspirin of 250 to 500 mg is recommended in aspirin-naïve patients; oral P2Y12 inhibitor pretreatment and loading doses are administered according to local standard of care. During the index procedure, heparin or bivalirudin is administered per standard practice and use of GPIIb/IIIa blockers is according to operator discretion.

After index procedure, DAPT is recommended for 1 month with a daily dose of aspirin (75-100 mg) and P2Y12 inhibitor (75 mg clopidogrel daily as the preferred regimen). For patients with a staged procedure within the prespecified 1 month, DAPT is prescribed for 1 month after the staged procedure. Patients treated with vitamin K anticoagulants or non–vitamin K anticoagulant oral antagonists may receive single antiplatelet therapy (SAPT) or DAPT from the date of the index procedure onward.

Beyond 1 month, SAPT is recommended with a daily dose of either 75 to 100 mg aspirin or 75 mg clopidogrel. Patients who have a stent thrombosis (or another adverse event where continued DAPT is needed) during the first 1 month may remain on DAPT beyond 1 month at the investigator's discretion.

Table II. Primary and secondary end points

End point	Time point(s) after index procedure
Primary end point	
Composite of cardiac death, MI, or stent thrombosis	1 y
Powered secondary end point	
TLF	1 y
Other secondary end points	
Composite of cardiac death, MI, and stent thrombosis	2 and 6 mo, 2 y
Acute success: device, lesion, and procedure	Index procedure
All deaths and cardiac deaths	1, 2, and 6 mo; 1 and 2 y
All MI and TVMI	1, 2, and 6 mo; 1 and 2 y
Stroke	1, 2, and 6 mo; 1 and 2 y
MACE	1, 2, and 6 mo; 1 and 2 y
TLF	2 and 6 mo, 1 and 2 y
TVF	1, 2, and 6 mo and 2 y
TLR, TVR, non-TVR	1, 2, and 6 mo; 1 and 2 y
Stent thrombosis	1, 2, and 6 mo; 1 and 2 y
Bleeding per BARC criteria	1, 2, and 6 mo; 1 and 2 y

Abbreviations: BARC, Bleeding Academic Research Consortium; TVF, target vessel failure.

End points

The primary end point is the composite of cardiac death, MI, or Academic Research Consortium (ARC) definite/probable stent thrombosis at 1 year after index procedure. The powered secondary end point is target lesion failure (TLF), defined as the composite of cardiac death, target vessel MI (TVMI), or clinically driven target lesion revascularization (TLR) by percutaneous or surgical methods, at 1 year after index procedure. All primary and secondary end points are listed in Table II.

Statistics

The primary end point in this trial is the composite of cardiac death, MI, or ARC definite/probable stent thrombosis at 1 year after index procedure. In the LEADERS FREE Study, the observed rate of this end point

for the BioFreedom stent was 9.4% (12). A noninferiority margin of 4.1% was selected for the current trial, representing 44% of the expected rate. Therefore, the null hypothesis is that the primary end point rate in the treatment arm (Resolute Onyx stent) will exceed that of the control arm (BioFreedom stent) by 4.1% or more. Assuming the true rate for both arms in the trial is 9.4%, with a 1-sided type I error of 0.05, an evaluable sample size of 900 patients in each arm yields more than 90% power. Assuming 10% loss to follow-up, a total sample size of up to 2,000 patients will be randomized. If noninferiority is established, a conditional test for superiority will be subsequently performed at the 1-sided .05 level.

If noninferiority for the primary end point is met, then the secondary end point of TLF at 1 year will be conditionally tested for noninferiority. The TLF rate in LEADERS FREE was not directly reported and was therefore estimated based on the reported components of TLF in that trial. At 1 year, the observed rates of cardiac death, MI and TLR with the BioFreedom stent were 4.2%, 6.1%, and 5.1%, respectively, so the TLF rate was conservatively estimated to be 11%. A noninferiority margin of 4.4% was selected, representing 40% of the expected rate. Noninferiority will be achieved if the upper limit of the 1-sided 95% CI of the difference is less than this margin. Assuming the true rates for both arms in the trial is 11%, with a 1-sided type I error of 0.05, an evaluable sample size of 900 patients in each arm yields more than 90% power. If noninferiority is established, a test for superiority will be subsequently performed at the 1-sided .05 level.

The primary analysis will be performed according to the intention-to-treat principle. All patients who are randomized will be considered part of the intention-to-treat population and will be followed up through the primary end point at 1 year. The per-protocol population consists of patients who received the treatment to which they were randomized but excluding patients who do not meet certain key inclusion criteria. The as-treated population consists of patients who are analyzed according to the stent type they received, rather than their randomization assignment. The primary and powered secondary end points will also be analyzed in the per-protocol and as-treated populations as secondary analyses.

Categorical variables will be tested using the Fisher exact or Cochran-Mantel-Haenszel tests as appropriate, and continuous variables will be tested using 2-sample *t* tests. Time to first event curves with Kaplan-Meier rate estimates will be generated with calculation of hazard ratios with 95% CIs. Subgroup analyses of the safety and efficacy end points will be performed for the following: acute coronary syndrome, diabetes mellitus, sex, age, and stent/lesion characteristics including multiple vessels, multiple lesions, and overlapping stents. The statistical analysis plan was written by the sponsor with input from the steering committee. All statistical analyses will be performed using SAS (version 9.1 or higher; SAS Institute, Cary, NC) by the sponsor, Medtronic, and independently validated by Baim Institute for Clinical Research (Boston, MA).

Definitions

Death is classified as cardiac death if due to immediate cardiac cause, including procedure-related deaths, as well as any unwitnessed death or death of unknown cause.

Myocardial infarction is defined according to the Third Universal Definition of Myocardial Infarction (28). Target vessel MI is defined as MI occurring in a territory that cannot be clearly attributed to a nontarget vessel.

Stroke is defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria, or other focal neurologic deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm. In addition, the stroke should persist more than 24 hours or result in death in the first 24 hours, be treated pharmacologically or nonpharmacologically, or have neuroradiologic diagnostic changes suggestive of acute tissue injury.

Clinically driven TLR/target vessel revascularization (TVR) are defined as revascularization at the target lesion/vessel associated with a positive functional ischemia study or ischemic symptoms, and an angiographic minimal lumen diameter stenosis $\geq$50% by quantitative coronary angiography or revascularization of a target lesion/vessel with diameter stenosis $\geq$70% by quantitative coronary angiography without either angina or positive functional study.

Target vessel failure is defined as cardiac death, TVMI, or clinically driven target TVR. Major adverse cardiac events include death, MI, or clinically driven TLR. Definitions from ARC were applied for both stent thrombosis and bleeding events (29,30). Specifically, stent thrombosis is defined as using the ARC definite or probable criteria, and bleeding is categorized by the Bleeding Academic Research Consortium criteria.

Acute lesion success is defined as attainment of <30% residual stenosis by quantitative coronary angiography (or <20% by visual assessment) and Thrombolysis in Myocardial Infarction flow 3 after the procedure, using any percutaneous method. Acute device success is defined as acute lesion success using only the assigned device. Acute procedural success is defined as acute lesion success without occurrence of MACE during the hospital stay.

Study limitations

Operators are not blinded to randomization; however, all personnel conducting follow-up will be blinded to randomization assignments to reduce bias. The CEC is also blinded to stent type. Results are specific to HBR

patients and may not be generalizable to the overall PCI population. The power calculation is based on event rates from a single trial, LEADERS-FREE. Therefore, although patient inclusion/exclusion criteria are very similar between the 2 trials, the observed event rates in LEADERS-FREE may have been influenced by chance, and differences in the event rates among BioFreedom-treated patients in the current trial may impact the power to determine non-inferiority to the Resolute Onyx DES. Finally, the results of the present study principally apply to patients in whom 1-month DAPT is believed to be appropriate based on bleeding risk and does not address the issue of optimal DAPT duration in this population.

Summary

The Onyx ONE global randomized trial is the first study to directly compare the safety and efficacy of 2 DES among HBR patients treated with 1 month of DAPT.

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Disclosures

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